NEUROIMMUNOLOGY

Myeloid cells in the central nervous system: So similar, yet so different

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Dissection of the heterogeneity of CNS myeloid cells reveals functionally distinct subsets that govern encephalitogenic T cells.

Myeloid immune cells populate the central nervous system (CNS) under homeostatic conditions. The CNS myeloid cell compartment is extremely heterogeneous, including perivascular, meningeal, and choroid plexus macrophages; dendritic cells (DCs); and microglia, among other populations. The complexity of this CNS innate immune cell compartment is amplified during inflammation, reflecting variable responses by CNS-resident myeloid cells and the recruitment of circulating myeloid cells into the inflamed CNS. These myeloid cell populations not only are heterogeneous with respect to their origin but also play multiple roles in health and disease. For example, microglia-driven synapse pruning plays an important role in CNS development but may also be an active player in neurologic disorders (*1*). Conversely, the presentation of cognate self-antigens by myeloid cells at CNS interfaces that reactivate encephalitogenic T cells is considered an important step in the pathogenesis of multiple sclerosis (MS) and its animal model, experimental autoimmune encephalomyelitis (EAE) (*2*). Thus, it is important to characterize CNS myeloid cell populations, their function, and the genomic programs that control them. Two new studies (*3*, *4*) shed fresh light on the heterogeneity and dynamics of myeloid cells in the CNS during EAE and their role in the reactivation of encephalitogenic T cells.

Jordão *et al.* (*4*) combined single-cell transcriptional analyses with fate mapping, clonal analyses, and transgenic mouse lines to characterize myeloid cells in the CNS during EAE. These studies identified previously unknown myeloid cell populations and candidate markers to monitor their function in CNS inflammation. Interestingly, the analysis of the local proliferation of CNS myeloid cells during EAE revealed the expansion of specific microglial clones (*4*), suggesting that yet undefined microglial subpopulations may be differentially regulated and play specific functions during autoimmune CNS inflammation (Fig. 1).

Pathogenic T cells must be reactivated by antigen-presenting cells (APCs) in the CNS to cross the blood-brain barrier, infiltrate the parenchyma, and cause immunopathology. Although previous studies identified $CD11c^+$ cells as APCs involved in the reactivation of encephalitogenic T cells (*2*), CD11c is expressed by several cell populations, including dendritic cells (DCs), microglia, border-associated macrophages, and monocytes. Thus, the specific APCs involved in the reactivation of pathogenic T cells remain unclear. To address this point, Mundt *et al.* (*3*) analyzed CNS $CD45^+$ $MHCII^+$ cells during EAE by means of mass cytometry (CyTOF) and elegantly evaluated the contribution of specific CNS myeloid cell populations to T cell reactivation using inducible Cre mouse lines to suppress major histocompatibility complex class II (MHC II) expression in target populations while minimizing off-target effects. These studies identified $CD11b^+$ $CD172a^+$ cDC2s as dominant APCs involved in the reactivation of encephalitogenic T cells during EAE and, potentially, MS. On the basis of their findings, Becher and coworkers propose a two-step model for T cell reactivation in CNS autoimmunity (Fig. 1): In the first step, T cells cross the endothelial cell barrier into the meninges in an antigen-independent manner. In the second step, the entry of encephalitogenic T cells into the CNS parenchyma to initiate disease requires the presentation of cognate antigens by cDC2s in the leptomeningeal space.

These studies are interesting not only because of the populations found to play a role in the reactivation of encephalitogenic T cells but also because of those found to be less relevant in this process. In particular, although microglia can potentially act as APCs, they were not found to have an essential role in T cell reactivation in the T cell–transfer EAE model used by Mundt *et al.* (*3*) nor in the model of EAE induced through active immunization used by Jordão *et al.* (*4*). These findings rule out a potential contribution of microglial APC function to the initiation of CNS autoimmunity but leave a window open for microglial APC function to participate in epitope spreading or the down-regulation of pathogenic T cell responses later in the disease process. Future studies should determine whether this is indeed the case and identify the specific microglial subpopulations involved.

These studies highlight the heterogeneity of CNS myeloid cells and suggest revisiting previous findings. For example, microglia control the activation of astrocytes, CNS-resident cells known to participate in the pathogenesis of neurologic disorders such as MS and Alzheimer's disease (*5*, *6*). Future studies should identify the specific microglial populations involved in the modulation of pathogenic and beneficial astrocytic responses in multiple contexts.

In addition, microglia are controlled by commensal bacteria, although the exact mechanisms involved are still unclear and have been proposed to involve the direct effects of microbial metabolites on microglia and/or the recruitment of microbiome-conditioned myeloid cells into the CNS (*6*–*8*). The data generated in these new studies should facilitate the identification of the specific myeloid cells and molecular mechanisms that participate in the control of microglia and other CNS-resident cells by the commensal flora and other environmental factors (*9*).

Together, these two studies provide important insights into the regulation of CNS inflammation and will certainly guide future investigations on the physiological roles of each of these CNS myeloid cell populations. These investigations should define the factors

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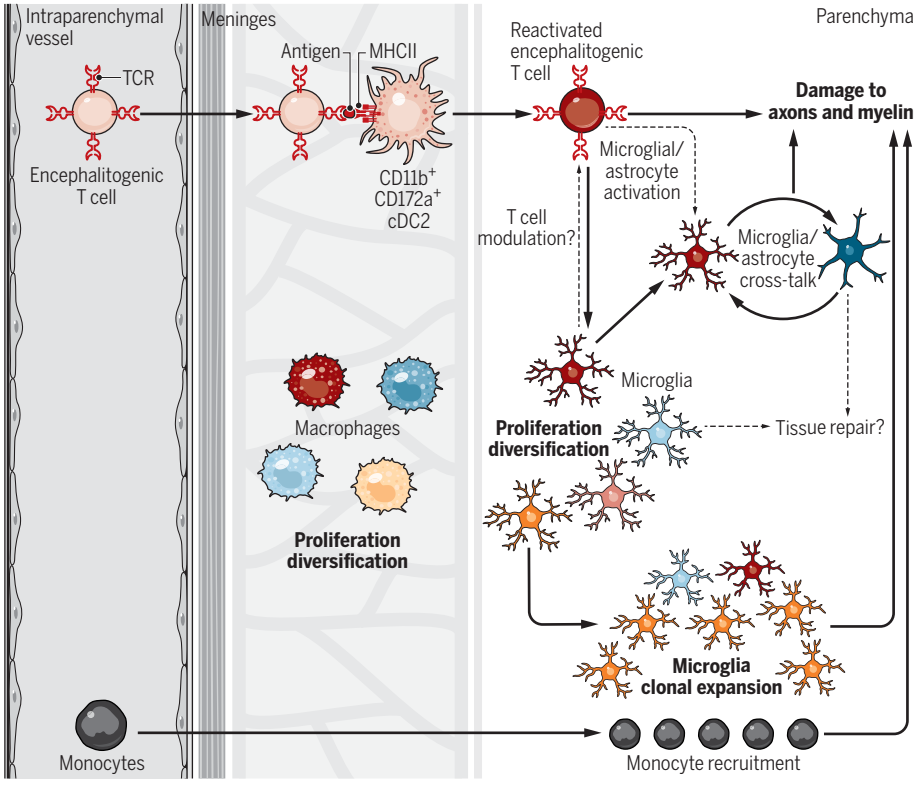

Fig. 1. A model for T cell–driven CNS pathology in MS. Encephalitogenic T cells cross the endothelial cell barrier into the meninges in an antigen-independent manner. After their reactivation by cDC2s presenting cognate self-antigens in the meninges, the encephalitogenic T cells enter into the CNS parenchyma to initiate processes that promote myelin and axonal damage, the activation of CNS myeloid cells, and the recruitment of additional peripheral myeloid cells, including monocytes. TCR, T cell receptor.

that drive the establishment and plasticity of these cell populations and the genomic programs that control them. In addition, these previously unidentified CNS myeloid cell populations and their associated transcriptional programs and surface markers provide an atlas that will facilitate the study of their contribution to the pathology of MS and their relationship to disease-associated cell populations that have been recently identified in other neurologic diseases (*10*). More importantly, the findings by Prinz, Becher, and collaborators might guide the development of highly needed therapeutic interventions for the modulation of CNS innate immunity in neurologic disorders (*3*, *4*).

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